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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/596,103	PETZELBAUER ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment filed after Non-final office action filed on May 4, 2009 is acknowledged. Claims 1-16 have been cancelled and new claims 17-28 have been added. Claims 17-28 are pending in this application.

Withdrawn Objection and Rejections

1. Objection to claim 7 is hereby withdrawn in view of Applicant's cancellation of claims 1-16.

2. Reject of claims 1-16 under 35 U.S.C. 112, second paragraph as being indefinite, is hereby withdrawn in view of Applicant's cancellation of claims 1-16.

3. Rejection of claims 1-16 under 35 U.S.C. 101, is hereby withdrawn in view of Applicant's cancellation of claims 1-16.

4. Rejection of claims 1-5 under 35 U.S.C. 102(b) as being anticipated by WO 99/02565 A (21, Jan. 1999, Therasorb Medizinische Systeme GMBH, used machined translated version), is hereby withdrawn in view of Applicant's cancellation of claims 1-16 and amendment to the claims.

5. Rejection of claims 1-4, 7-12 and 15-16 under 35 U.S.C. 102(b) as being anticipated by Dean et al (WO 9317719 A1), is hereby withdrawn in view of Applicant's cancellation of claims 1-16 and amendment to the claims.

6. Rejection of claims 1-4, 7-12 and 15-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Dean et al (US patent No. 5,720,934), is hereby withdrawn in view of Applicant's cancellation of claims 1-16 and amendment to the claims.

7. Rejection of claims 1-4, 7-12 and 14-16 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-25 of copending Application No. 11/542,050, is hereby withdrawn in view of Applicant's cancellation of claims 1-16 and amendment to the claims. However, a revised double patenting rejection unpatentable over US Patent No. 7,494,973 follows below.

8. Rejection of claims 1-4, 7-12 and 14-16 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8-10, 14-25 of copending Application No. 11/678,535 (US 2008/0039388 A1), is hereby withdrawn in view of Applicant's cancellation of claims 1-16 and amendment to the claims.

9. Rejection of claims 1-4, 7-12 and 14-16 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-25 of copending Application No. 12/248,656, is hereby withdrawn in view of Applicant's cancellation of claims 1-16 and amendment to the claims.

10. Rejection of claims 1-4, 7-12 and 14-16 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8-14 of copending Application No. 12/280,543, is hereby withdrawn in view of Applicant's cancellation of claims 1-16 and amendment to the claims.

Maintained and Revised Rejections

35 USC § 112,2nd

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 17-20, 23-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 17, 19-20 recite, “residue” which is indefinite. It is unclear what is encompassed by the term “residue.” The specification does not define what is encompassed by the term residue. The dictionary defines “residue” as “1. something that remains after a part is removed, disposed of, or used; remainder; rest; remnant; 2b. an atom or group of atoms considered as a group or part of a molecule; 2c. that part remaining as a solid on a filter paper after a liquid passes through in the filtration procedure” (see http://dictionary.reference.com/browse/residue). Therefore, it is unclear what is meant by the term "residue" and what is encompassed by the term "residue". Because claims 18-20 and 23-26 depend from indefinite claim 17 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

35 U.S.C. 112, 1st

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 17-18 and 23-24 are rejected are under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (5) the breadth of the claims:

The claims are drawn to a method for treating shock comprising administering to a subject in need of such treatment an effective amount of a peptide of Formula II, wherein Z_5 denotes a peptide derived from the Bbeta chain of the fibrin, which peptide has the biological property of matching the inducible VE-cadherin binding motif on the Bβ-chain of human fibrin.

(2) The state of the prior art and (4) the predictability or unpredictability of the art::

With regards to the effect of amino acid substitution in a peptide or protein, the art is unpredictable.

Rudinger (Peptide Hormones, JA Parsons, Ed., 1976, 1-7) teaches that, "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study" (see p. 6). Additionally, SIGMA states that with regards to design of peptide sequences that, "Even for relatively short sequences, there are essential and non-essential (or less important) amino acid residues, although the relative importance of the individual amino acid residues is not always easy to determine" (see p. 1). SIGMA further describes what effect some substitutions may have, rather than what effect they will have on hydrophobicity, secondary structure (which will affect tertiary and quaternary structure), and solubility. Additionally, Schinzel et al (FEBS, 1991, 286(1, 2): 125-128) teach that the substitution of Lys^{539} by an arginine caused a 600 fold reduction, substitution of Arg^{534} by a glutamine caused an even larger 7000-fold reduction of the catalytic rate while substrate binding remained essentially unaffected. The reference teaches that Arg^{534} to Gln exchange reduces the catalytic rate near to inactivity and even the conservative Lys^{534} to Arg exchange caused marked decrease of activity (see abstract).

With regards to prediction of the native conformation of a protein (structure), the art is unpredictable. Berendsen (Science, 1998, 282: 642-643) states, "The prediction of the native conformation of a protein of known amino acid sequence is one of the great

open questions in molecular biology and one of the most demanding challenges in the new field of bioinformatics" (see p. 642). Furthermore, Berendsen states that "Folding to the stable native state [computationally] has not (yet) occurred, and the simulations do not contain any relevant statistics on the process. The real protein will fold and refold hundreds to thousands of times until it stumbles into the stable conformation with the lowest free energy. Because this hasn't happened (and couldn't happen) in the simulations, we still cannot be sure of the full adequacy of the force field" (see p. 642).

Further, the effects of a single amino acid substitution can have substantial effects on proteins in structure and/or function and are exemplified by the difference between hemoglobin (Hb) and abnormal hemoglobins, such as sickle-cell hemoglobin (HbS). Voet et al teaches that the mutant hemoglobin HbE [GluB8(26)β to Lys] has, "no clinical manifestations in either heterozygotes or homozygotes" (see p. 235). Further, Hb Boston and Hb Milwaukee both have single point mutations which results in altered binding affinity and ineffective transfer from the Fe(III) to Fe(II) oxidation state. Conversely, a single point mutation in Hb Yakima results in increased oxygen binding by the heme core, and in Hb Kansas, the mutation causes the heme center to remain in the T state upon binding oxygen (rather than structurally rearranging to the R state) (see p. 236). Further, HbS is a single point mutation, Val to GluA3(6)β (see p. 236), which results in deformation and rigidity of the red blood cell. The mutation also provides protection against most malarial strains.

As with all peptides, activity is based on the structure of the peptide. That is, the peptide has to have the proper structure to recognize the specific receptor for the

peptide to be active. The sate of the art for prediction of the native conformation of the protein is, at best, a vague science. For example, in peptide chemistry, Ngo et al teach that for protein and peptides, a "'Direct' approach to structure prediction, that of directly simulating the folding process, is not yet possible because contemporary hardware falls eight to nine orders of magnitude short of the task" (see p. 493). Accordingly, it is not known if an efficient algorithm for predicting the structure exists for a protein or peptide from its amino acid alone (see p. 492). Thus, activity of a given peptide cannot be based on its structure alone. Similarly, the Rudinger article (see the conclusion in particular) states "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study." Finally, in an article published in Science, the author concluded that "one of the 'grand challenges' of high-performance computing-predicting the structure of proteins-acquires much of the flavor of the Holy Grail-quest of the legendary knights of King Arthur. It is extremely desirable to possess but extremely elusive to obtain" (see p. 643 in Berendsen). Berendsen et al states "at the present level of sophistication, [homology modeling] are effective for only 25% of the proteins for which the amino acid sequence is known" (see p. 642). It is known that proteins fold into their native conformation spontaneously and within seconds. The underlying principle of folding is known in the art yet the art lacks the ability to mimic native folding process (see p. 642 in Berendsen). "[E]xisting computers cannot sample enough configurations in a reasonable time to come up with the thermodynamically stable native structure;…we are not too sure that the available force field descriptions, which we need

to compute the energy of a each configuration, are accurate enough to come up with reliable free energy of a conformation" (see p. 642 in Berendsen). Berendsen et al discloses the principle of the "Levinthal's paradox" which states that if one was to assume that "three possible states for every flexible dihedral angle in the backbone of a 100 protein residue, the number of possible backbone configuration is 3^{200}. Even an incredibly fast computational or physical sample in 10^{-15}s would mean that complete sample would take 10^{80}s, which excides that age of the universe by more than 60 orders of magnitude." Other tools such as lattice models provide insight into principle of folding, but to provide no solutions to the real folding problems (see p. 643 in Berendsen). The art has recognized that even single point mutations can cause diverse effects on peptide activity. It has been shown in numerous peptides that a single amino acid can have deleterious effects on the peptide. For example, Bradley et al teach that a single substitution of Ala to Gly in six analogous structural peptides of an ankyrin protein resulted in dramatic and diverse effects on protein stability (see Bradley et al). Sickle cell anemia can be traced to a single point mutation at position six in the beta globulin protein.

Additionally, Skolnick et al. (Trends in Biotechnology, 2000. Vol. 18, pages 34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., Abstract and Sequence-based approaches to function prediction, page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental

research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular Abstract and Box 2). The instant application claims are open to any amino acid modification at any position of any therapeutic polypeptides. The working examples given do not sufficiently establish whether any peptide encompassed by the claimed invention would behave similarly. Given that point mutations can lead to abolishment of activity, one would be burdened with undue experimentation to screen the numerous compounds in attempting to find those that have the same activity as the wild-type therapeutic polypeptides.

Given that one could not determine the structure of a protein computationally, and that the effect of amino acid substitution is unpredictable, it flows logically that one would be unduly burdened with experimentation to determine the effect of amino acid substitution(s) in a peptide or protein, with regards to structure, function, or physical/chemical properties. The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined on a case by case basis requiring experimental study, as described above. Since the claims broadly encompass any peptide or peptidomimetic, it is not clearly evident how one can predict any peptide forming such a distinct peptide formulation having required efficacy. In other words, not all peptides would form a functional therapeutic compound claimed. Therefore, how one can effectively predict a method of preparing a pharmaceutical preparation comprising formula II (wherein Z_5 peptide has the biological property of matching the inducible VE-cadherin binding motif of the Bβ-chain of human fibrin) of any peptide having such distinct properties that will be equally

effective no matter what peptide is utilized is not clearly evident. Therefore, making any polypeptide having any lengths amino acids that has the same activity as the claimed polypeptide, one would be unduly burdened with experimentation to determine the effect of amino acid content, substitution(s), addition and deletions in a peptide or protein, with regards to structure, function, or physical/chemical properties.

(3) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples:

The specification describes that the Z1 denotes a histidine or proline moiety and Z2 of formula I denotes an arginine moiety, a peptide moiety or a protein moiety comprising an initial arginine moiety, in particular comprising from 2 to 30 amino acids, which peptide has the biological property of matching the inducible VE-cadherin binding motif on the Bβ chain of human fibrin (see paragraph [0010] of instant specification 2008/0249006 A1). The specification describes that the Z5 of general formula II denotes a peptide moiety or a protein moiety in particular comprising from 2 to 30 amino acids or an alcohol moiety comprising from 1 to 10, in particular from 1 to 3, carbon atoms or an organic or inorganic base moiety (see paragraph [0011] of instant specification as described above). The specification further describes that a peptide is preferably used in which Z5 is a peptide moiety comprising the amino acid sequence

DKKREEAPSLRPAPPISGGGYR (see paragraph [0013] of instant specification as described above). The specification further discloses that Z5 is a peptide moiety comprising the amino acid sequence ERHQSACKDSDWPFCSDEDWNYK, Z1 is a proline moiety, Arg is an arginine moiety, Z3 is a valine moiety, and Z4 is valine moiety (see paragraph [0014] of instant specification as described above). Additionally, the specification discloses that the N-terminal sequence is GHRPLDKKREEAPSLRPAPPPISGGGYR (see paragraph [0015] of instant specification as described above). The specification discloses that the peptides were produced by a solid-phase peptide synthesis and purified with reversed-phase HPLC (see paragraph [0018] of instant specification as described above).

The working example describes the treatment of inbred four-week old male BALB/c mice that were infected with mouse-adapted DEN-2 strain P23085. The treatment was performed with peptide Bb15-42 twice per day by intraperitoneal injection (4800 μg/kg each) from day 3-post infection to day 8-post infection (see paragraphs [0030]-[0031]). The specification further describes the treatment of gram-negative shock on rats (see paragraphs [0032]-[0037]). The specification further discloses that "a modified ELISA is not to quantify fibrin degradation products but to search for proteins, peptides or compounds which interfere with the binding of the Bβ15-42 sequence and the VE-cadherin (see paragraph [0021]). Further, the specification discloses that 96 well protein immobilizer plates were coated with recombinant human VE-cadhein FC fusion protein in PBS. The plates were then washed and incubated with peptide Bβ15-42 (GHRPLDKKREEAPSLRAPPPISGGGYR) tagged with a FLAG-sequence

(DYKDDDDDK) at the C-terminus of the peptide or with a FLAG-tagged random peptide (DRGAPAHRPPRGPISGRSTPEKEKLLPG). After washing, bound FLAG-tagged peptide was detected by incubation with a peroxidase-labelled anti-FLAG antibody and chromogenic substrate (see paragraphs [0021]-[0023]).

The specification does not describe how to maintain the functionality of all of the polypeptide and what amino acids are required to have therapeutic effect. Description of FLAG-tagged random peptide or FLAG-tagged sequence is not sufficient to encompass numerous other peptides and polypeptide that belong to the same genus. For example, there are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus. For a peptide having 25 amino acids, there would be $25^{20} = 9.09 \times 10^{27}$ different oligopeptide possibilities. For a peptide having 30 amino acids, there would be $30^{20} = 3.5 \times 10^{29}$ different peptide possibilities. If moiety is considered as any addition, substitution and/or deletion, this number increases. The specification however, does not provide for the vast number of polypeptide embraced by the broad genus claimed. There is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed. Since there are 20 naturally occurring amino acids, the possibilities are limitless.

Additionally, the art recognizes that “The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study”. Additionally, SIGMA states that with regards to design of peptide sequences that, “Even for relatively short sequences, there are essential and non-essential (or less important) amino acid

residues, although the relative importance of the individual amino acid residues is not always easy to determine" (see p. 1). SIGMA further describes what effect some substitutions may have, rather than what effect they will have on hydrophobicity, secondary structure (which will affect tertiary and quaternary structure), and solubility. Therefore, any modification on the polypeptide might have an affect on the polypeptide, thus vast numbers of experimentation would be required to see if the polypeptide would have the same affect on certain diseases as the wild-type polypeptide. Furthermore, modification of therapeutic polypeptide incorporating the general formula I or II is not known to maintain the therapeutic effectiveness for ALL polypeptides. Thus, vast numbers of experimentation would be required to see if the polypeptide comprising different amino acid substitution would have the same affect on treatment of shock as the wild-type polypeptides.

As with all peptides, activity is based on the structure of the peptide. That is, the peptide has to have the proper structure to recognize the specific receptor for the peptide to be active. The sate of the art for prediction of the native conformation of the protein is, at best, a vague science. For example, in peptide chemistry, Ngo et al teach that for protein and peptides, a "'Direct' approach to structure prediction, that of directly simulating the folding process, is not yet possible because contemporary hardware falls eight to nine orders of magnitude short of the task" (see p. 493). Accordingly, it is not known if an efficient algorithm for predicting the structure exists for a protein or peptide from its amino acid alone (see p. 492). Thus, activity of a given peptide cannot be based on its structure alone. Similarly, the Rudinger article (see the conclusion in particular)

states “The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study.” Finally, in an article published in Science, the author concluded that “one of the ‘grand challenges’ of high-performance computing-predicting the structure of proteins-acquires much of the flavor of the Holy Grail-quest of the legendary knights of King Arthur. It is extremely desirable to possess but extremely elusive to obtain" (see p. 643 in Berendsen). Berendsen et al states “at the present level of sophistication, [homology modeling] are effective for only 25% of the proteins for which the amino acid sequence is known” (see p. 642). It is known that proteins fold into their native conformation spontaneously and within seconds. The underlying principle of folding is known in the art yet the art lacks the ability to mimic native folding process (see p. 642 in Berendsen). “[E]xisting computers cannot sample enough configurations in a reasonable time to come up with the thermodynamically stable native structure;…we are not too sure that the available force field descriptions, which we need to compute the energy of a each configuration, are accurate enough to come up with reliable free energy of a conformation" (see p. 642 in Berendsen). Berendsen et al discloses the principle of the "Levinthal's paradox" which states that if one was to assume that "three possible states for every flexible dihedral angle in the backbone of a 100 protein residue, the number of possible backbone configuration is 3^{200}. Even an incredibly fast computational or physical sample in 10^{-15}s would mean that complete sample would take 10^{80}s, which excides that age of the universe by more than 60 orders of magnitude.” Other tools such as lattice models provide insight into principle of

folding, but to provide no solutions to the real folding problems (see p. 643 in Berendsen). The art has recognized that even single point mutations can cause diverse effects on peptide activity. It has been shown in numerous peptides that a single amino acid can have deleterious effects on the peptide. For example, Bradley et al teach that a single substitution of Ala to Gly in six analogous structural peptides of an ankyrin protein resulted in dramatic and diverse effects on protein stability (see Bradley et al). Sickle cell anemia can be traced to a single point mutation at position six in the beta globulin protein. The working examples given do not sufficiently establish whether any peptide encompassed by the claimed invention would behave similarly. Given that point mutations can lead to abolishment of activity, one would be burdened with undue experimentation to screen the numerous compounds in attempting to find those that have the same activity as the wild-type therapeutic polypeptides.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the reference above and the high unpredictability and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to make amino acid modification for all polypeptides of general formula II that maintain the function of the therapeutic polypeptide.

15. Claims 17-18 and 23-24 are rejected are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The MPEP

states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but

not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to the use of a peptide of general formulae I and II...for the preparation of a pharmaceutical preparation for the treatment of shock. The claims are further drawn to a peptide having N-terminus of SEQ ID NO: 3. The generic statements peptide of general formulae I and II do not provide ample written description for the compounds since the claims do not describe a single structural feature. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention.

As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claims 1 and 2 are broad generics with respect all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of peptide or a peptide-like molecule that can form peptide or amide bonds. It must not be forgotten that the MPEP states that if a peptide is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives. The specification is void of organic molecules that functions as a peptide-like molecule that qualify for the functional characteristics claimed as a polypeptide or a peptide-like molecule or other peptidic molecules that contains Formula (II), and other synthetic peptide or peptide-like molecule that can function as these compounds. There are innumerable numbers of therapeutic polypeptide. Furthermore, a modified therapeutic polypeptide can have different amino acid sequences, variants, homologs, etc, therefore, there are even greater numbers of possibilities for polypeptide comprising the amino acid structure of formula II.

The specification is limited to the certain amino acids or peptide-like molecules that are used to form the polypeptide of formulae I and II. The specification describes that the Z1 denotes a histidine or proline moiety and Z2 of formula I denotes an arginine moiety, a peptide moiety or a protein moiety comprising an initial arginine moiety, in particular comprising from 2 to 30 amino acids, which peptide has the biological property of matching the inducible VE-cadherin binding motif on the Bβ chain of human fibrin (see paragraph [0010] of instant specification 2008/0249006 A1). The specification describes that the Z5 of general formula II denotes a peptide moiety or a protein moiety in particular comprising from 2 to 30 amino acids or an alcohol moiety comprising from 1 to 10, in particular from 1 to 3, carbon atoms or an organic or inorganic base moiety (see paragraph [0011] of instant specification as described above). The specification further describes that a peptide is preferably used in which Z5 is a peptide moiety comprising the amino acid sequence DKKREEAPSLRPAPPISGGGYR (see paragraph [0013] of instant specification as described above). The specification further discloses that Z5 is a peptide moiety comprising the amino acid sequence ERHQSACKDSDWPFCSDEDWNYK, Z1 is a proline moiety, Arg is an arginine moiety, Z3 is a valine moiety, and Z4 is valine moiety (see paragraph [0014] of instant specification as described above). Additionally, the specification discloses that the N-terminal sequence is GHRPLDKKREEAPSLRPAPPPISGGGYR (see paragraph [0015] of instant specification as described above). The specification discloses that the peptides were produced by a solid-phase peptide synthesis and purified with reversed-phase HPLC (see paragraph [0018] of instant specification as described above).

The working example describes the treatment of inbred four-week old male BALB/c mice that were infected with mouse-adapted DEN-2 strain P23085. The treatment was performed with peptide Bβ15-42 twice per day by intraperitoneal injection (4800 μg/kg each) from day 3-post infection to day 8-post infection (see paragraphs [0030]-[0031]). The specification further describes the treatment of gram-negative shock on rats (see paragraphs [0032]-[0037]). The specification further discloses that "a modified ELISA is not to quantify fibrin degradation products but to search for proteins, peptides or compounds which interfere with the binding of the Bβ15-42 sequence and the VE-cadherin (see paragraph [0021]). Further, the specification discloses that 96 well protein immobilizer plates were coated with recombinant human VE-cadhein FC fusion protein in PBS. The plates were then washed and incubated with peptide Bβ15-42 (GHRPLDKKREEAPSLRAPPPISGGGYR) tagged with a FLAG-sequence (DYKDDDDDK) at the C-terminus of the peptide or with a FLAG-tagged random peptide (DRGAPAHRPPRGPISGRSTPEKEKLLPG). After washing, bound FLAG-tagged peptide was detected by incubation with a peroxidase-labelled anti-FLAG antibody and chromogenic substrate (see paragraphs [0021]-[0023]).

The specification does not describe how to maintain the functionality of all of the polypeptide and what amino acids are required to have therapeutic effect. Description of FLAG-tagged random peptide or FLAG-tagged sequence is not sufficient to encompass numerous other peptides and polypeptide that belong to the same genus. For example, there are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus. For a peptide having 25 amino acids, there would be

25^{20} = 9.09 X 10^{27} different oligopeptide possibilities. For a peptide having 30 amino acids, there would be 30^{20} = 3.5 X 10^{29} different peptide possibilities. If moiety is considered as any addition, substitution and/or deletion, this number increases. The specification however, does not provide for the vast number of polypeptide embraced by the broad genus claimed. There is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed. Since there are 20 naturally occurring amino acids, the possibilities are limitless. There are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus of therapeutic polypeptide. This leads to innumerable possible variations of compounds that can be formed. For example, each substitution, addition, deletion of the polypeptide would lead to a different protein having different structure and different function. For example, Skolnick et al. (Trends in Biotechnology, 2000. Vol. 18, pages 34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., Abstract and Sequence-based approaches to function prediction, page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular Abstract and Box 2). Furthermore, there are no examples of what a residue of histidine, arginine, proline or valine, leucine or valine and so on in relation to formula (II). There is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Response to Applicant's Arguments

16. Applicant argues that "claims 1-16 have been cancelled and replaced with new claims 17-28, which are drawn to a method for treating shock."

17. Applicant's arguments have been fully considered but have not been found persuasive, since newly added claims are drawn to a method for treating shock comprising administering to a subject in need of such treatment an effective amount of a peptide of Formula II...wherein Z_5 denotes a peptide derived from the Bbeta chain of the fibrin, which peptide has the biological property of matching the inducible VE-cadherin binding motif on the Bβ-chain of human fibrin. The specification does not describe how to maintain the functionality of all of the polypeptide and what amino acids are required to have therapeutic effect. Furthermore, it is unclear what peptide derived from the Bbeta chain of the fibrin would have the biological property of matching the inducible

VE-cadherin binding motif on the Bbeta-chain of human fibrin. For a peptide having 25 amino acids, there would be $25^{20} = 9.09 \times 10^{27}$ different oligopeptide possibilities. For a peptide having 30 amino acids, there would be $30^{20} = 3.5 \times 10^{29}$ different peptide possibilities. If moiety is considered as any addition, substitution and/or deletion, this number increases. The specification however, does not provide for the vast number of polypeptide embraced by the broad genus claimed. Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Furthermore, the art has recognized that even single point mutations can cause diverse effects on peptide activity. It has been shown in numerous peptides that a single amino acid can have deleterious effects on the peptide. For example, Bradley et al teach that a single substitution of Ala to Gly in six analogous structural peptides of an ankyrin protein resulted in dramatic and diverse effects on protein stability (see Bradley et al). Sickle cell anemia can be traced to a single point mutation at position six in the beta globulin protein. The working examples given do not sufficiently establish whether any peptide encompassed by the claimed invention would behave similarly. Given that point mutations can lead to abolishment of activity, one would be burdened with undue experimentation to screen the numerous compounds in attempting to find those that have the same activity as the wild-type therapeutic polypeptides. The art has recognized that even single point mutations can cause diverse effects on peptide

activity. It has been shown in numerous peptides that a single amino acid can have deleterious effects on the peptide. For example, Bradley et al teach that a single substitution of Ala to Gly in six analogous structural peptides of an ankyrin protein resulted in dramatic and diverse effects on protein stability (see Bradley et al). Sickle cell anemia can be traced to a single point mutation at position six in the beta globulin protein. The working examples given do not sufficiently establish whether any peptide encompassed by the claimed invention would behave similarly. Given that point mutations can lead to abolishment of activity, one would be burdened with undue experimentation to screen the numerous compounds in attempting to find those that have the same activity as the wild-type therapeutic polypeptides.

Revised Rejection-35 U.S.C. 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

19. Claims 17-28 are rejected under 35 U.S.C. 102(a) as being anticipated by Petzelbauer P (US 2004/0192596 A1).

20. Petzelbauer teaches the same formulae I and II as the instant formula II, see paragraphs [0002] and [0006]. Furthermore, GHRPLDKKREEAPSLRPAPPPISGGGYR

(see SEQ ID NO: 294) that is the same as the one claimed in instant claims 17-22 and the instant SEQ ID NOS: 2 and 3, meeting the limitation of claims 17-22. Furthermore, the instant claims 23-28 recite "…wherein the shock is associated with one or more groups comprising bacterial toxins, haemorrhagic shock following viral infection…infectious agents or autoimmune diseases, organ failure…and so on. (see claims 23-28). Petzelbauer reference teaches the method of preventing inflammation in a subject comprising administering to the subject an effective amount of a peptide having the general formula II, wherein the inflammation is due to a condition selected from the group consisting of an infection, an autoimmune condition, a rheumatic disorder, or a disorder of the immune system (see claims 14 and 21). Since the cause that leads to inflammation and shock is the same, the method of treating inflammation would necessarily treat shock, and vice versa.

21. Claims 17-28 are rejected under 35 U.S.C. 102(e) as being anticipated by Petzelbauer P (US 2004/0192596 A1).

22. Petzelbauer teaches the same formulae I and II as the instant formula II, see paragraphs [0002] and [0006]. Furthermore, GHRPLDKKREEAPSLRPAPPPISGGGYR (see SEQ ID NO: 294) that is the same as the one claimed in instant claims 17-22 and the instant SEQ ID NOS: 2 and 3, meeting the limitation of claims 17-22. Furthermore, the instant claims 23-28 recite "…wherein the shock is associated with one or more groups comprising bacterial toxins, haemorrhagic shock following viral infection…infectious agents or autoimmune diseases, organ failure…and so on (see

claims 23-28). Petzelbauer reference teaches the method of preventing inflammation in a subject comprising administering to the subject an effective amount of a peptide having the general formula II, wherein the inflammation is due to a condition selected from the group consisting of an infection, an autoimmune condition, a rheumatic disorder, or a disorder of the immune system (see claims 14 and 21). Since the cause that leads to inflammation and shock is the same, the method of treating inflammation would necessarily treat shock, and vice versa.

Response to Applicant's Arguments

23. Applicant argues that "claims 1-5 have been cancelled, thereby rending the rejection moot. Additionally, Applicant asserts that Petzelbauer does not teach each and every element of the presently pending claims 17-28…Petzelbauer does not teach any method for treating shock, and thereby cannot teach a method of treating shock by administering the substance of Formula II."

24. Applicant's arguments have been fully considered have not been found persuasive. Petzelbauer teaches a method of treating inflammation, which is due to the same conditions as the instant claims. According to claims 21 of Petzelbauer reference, the inflammation is due to a condition selected from the group consisting of an infection, an autoimmune condition, a rheumatic disorder, or a disorder of the immune system. Since the cause of the shock is the same as the cause of inflammation, this reference anticipates claims 17-28.

25. Claims 17-28 are rejected under 35 U.S.C. 102(a) as being anticipated by Petzelbauer P (US 2007/0037749 A1).

26. Petzelbauer teaches the same formula II as the instant formula II, see paragraphs [0007] and [0011]. Furthermore, the reference teaches the sequences GHRPLDKKREEAPSLRPAPPPISGGGYR (see SEQ ID NO: 294) that is the same as the one claimed in instant claims 17-22 and the instant SEQ ID NOS: 2 and 3, meeting the limitation of claims 17-22. The reference teaches that the invention consist of the preparation of pharmaceutical compositions for the therapy or prevention of local and/or generalized inflammations in the body in case of infectious genesis, based upon autoimmune reaction, based upon a rheumatic disease, based upon a disorder in the immune system…for the prevention and/or therapy of the rejection occurring after organ transplants…" (see paragraph [0034]). The instant claims 23-28 recite "…wherein the shock is associated with one or more groups comprising bacterial toxins, haemorrhagic shock following viral infection…infectious agents or autoimmune diseases, organ failure…and so on (see claims 23-28). Claim 3 of the reference claims that the inflammation is due to a condition selected from the group consisting of an infection, an autoimmune condition, a rheumatic disorder, or a disorder of the immune system (see claim 3). Since the cause that leads to inflammation and shock is the same, and the reference claims a method of treating inflammation in a subject (see claims 1-4), a method of inhibiting inflammation of a transplanted tissue in a subject (see claims 5-6), the method of treating inflammation and inhibiting inflammation in a transplanted tissue would necessarily treat shock, and vice versa.

27. Claims 17-28 are rejected under 35 U.S.C. 102(e) as being anticipated by Petzelbauer P (US 2007/0037749 A1).

28. Petzelbauer teaches the same formula II as the instant formula II, see paragraphs [0007] and [0011]. Furthermore, the reference teaches the sequences GHRPLDKKREEAPSLRPAPPPISGGGYR (see SEQ ID NO: 294) that is the same as the one claimed in instant claims 17-22 and the instant SEQ ID NOS: 2 and 3, meeting the limitation of claims 17-22. The reference teaches that the invention consist of the preparation of pharmaceutical compositions for the therapy or prevention of local and/or generalized inflammations in the body in case of infectious genesis, based upon autoimmune reaction, based upon a rheumatic disease, based upon a disorder in the immune system…for the prevention and/or therapy of the rejection occurring after organ transplants…" (see paragraph [0034]). The instant claims 23-28 recite "…wherein the shock is associated with one or more groups comprising bacterial toxins, haemorrhagic shock following viral infection…infectious agents or autoimmune diseases, organ failure…and so on (see claims 23-28). Claim 3 of the reference claims that the inflammation is due to a condition selected from the group consisting of an infection, an autoimmune condition, a rheumatic disorder, or a disorder of the immune system (see claim 3). Since the cause that leads to inflammation and shock is the same, and the reference claims a method of treating inflammation in a subject (see claims 1-4), a method of inhibiting inflammation of a transplanted tissue in a subject (see claims 5-6), the method of treating inflammation and inhibiting inflammation in a transplanted tissue would necessarily treat shock, and vice versa.

Response to Applicant's Arguments

29. Applicant argues that "claims 1-5 have been cancelled, thereby rending the rejection moot. Additionally, Applicant asserts that Petzelbauer II does not teach each and every element of the presently pending claims 17-28…Petzelbauer does not teach or suggest any method for treatment of any of the conditions recited in claims 23-28.

30. Applicant's arguments have been fully considered but have not been found persuasive. Petzelbauer teaches a method of treating inflammation, which is due to the same conditions as the instant claims. According to claim 3 of Petzelbauer reference, the inflammation is due to a condition selected from the group consisting of an infection, an autoimmune condition, a rheumatic disorder, or a disorder of the immune system. According to claim 5 of the Petzelbauer reference, inflammation is due to a transplanted tissue. The instant claims 23-28 recite bacterial toxins, viral infection, infectious agents, autoimmune disease, organ failure after organ injury...organ dysfunction of grafted organs, and so forth. Since the cause of the shock is the same as the cause of inflammation, this reference anticipates claims 17-28.

Revised Obviousness Double Patenting

31. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

32. Claims 17-28 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 7,271,144. Although the conflicting claims are not identical, they are not patentably distinct from each other because if one practiced the claimed invention of instant application, one would achieve the claimed invention of U.S. Patent No. '144 and vice versa.

33. Instant claims are drawn to a method for treating shock comprising administering to a subject in need of such treatment an effective amount of a peptide of Formula II.

34. Claims 1-4 of U.S. Patent No. '144 are drawn to a method of treating inflammation in a subject comprising administering to the subject a peptide of SEQ ID NO: 294, wherein the inflammation is due to a condition selected from the group consisting of an infection, an autoimmune condition, a rheumatic disorder, or a disorder of the immune system.

35. U.S. Patent No. '144 claims the peptide of formula II of the instant claims, and teaches a method of treating inflammation in a subject comprising administering to the subject a peptide SEQ ID NO: 294, which is the same as the instant claims 17-22, and also teaches that the inflammation is due to the same conditions (infection, autoimmune

disease, a rheumatoid disorder, or a disorder of the immune system) (see claim 3). Therefore, if one practiced the claimed invention of the instant claims, one would necessarily achieve the claimed invention of the U.S. Patent No. '144 and vice versa.

Response to Applicant's Arguments

36. Applicant argues that "none of claims 1-4 of the '144 patent claim, teach or suggest anything related to stress or methods for treating stress."

37. Applicant's arguments have been fully considered but have not been found persuasive. Instant claims 23-26 recite the cause associated with shock, including bacterial toxins, autoimmune diseases, organ failure, infectious agents, vascular surgery, organ dysfunction, and so on. Claim 3 of Patent '144 claims that the method of treating inflammation is due to a condition selected from the group consisting of an infection, an autoimmune condition, a rheumatic disorder, or a disorder of the immune system. Since the cause of shock and inflammation are due to the same conditions, US Patent '144 clearly envisions the use of peptide SEQ ID NO: 294 for the treatment of shock.

38. Claims 17-28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of copending Application No. 11/899,611. Although the conflicting claims are not identical, they are not patentably distinct from each other because if one practiced the claimed invention of instant claims, one would necessarily achieve the claimed invention of copending application and vice versa.

39. Instant claims are drawn to a method for treating shock comprising administering to a subject in need of such treatment an effective amount of a peptide of Formula II. Claims 23-28 are drawn to a method of treating shock, wherein shock is due to myocardial infarction, vascular surgery...surgical procedures and stroke, and organ dysfunction of grafter organs, and so forth.

40. Claims 1-4 of copending application are drawn to a method of treating reperfusion injury in a subject comprising administering to the subject a peptide of SEQ ID NO:294, that is the same as the instant SEQ ID NO:3. The specification of the reference discloses that a healing effect occurs with a drug for the therapy and/or prevention of a reperfusion trauma following a surgically or pharmaceutically induced restoration of the blood flow such as, after cardiac infarction, apoplectic stroke, after vascular surgery…(see paragraph [0066] of instant specification US 2009/0137464 A1).

41. Therefore, if one of ordinary skill in the art practiced the claimed invention of the instant claims, one would necessarily achieve the claimed invention of copending application 11/899,611, and vice versa.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Applicant's Arguments

42. Applicant has not provided any arguments for this obviousness rejection.

43. As described above in the body of the rejection, claims 1-4 of copending application are drawn to a method of treating reperfusion injury in a subject comprising administering to the subject a peptide of SEQ ID NO:294, that is the same as the instant

SEQ ID NO:3. The specification of the reference discloses that a healing effect occurs with a drug for the therapy and/or prevention of a reperfusion trauma following a surgically or pharmaceutically induced restoration of the blood flow such as, after cardiac infarction, apoplectic stroke, after vascular surgery…(see paragraph [0066] of instant specification US 2009/0137464 A1). Since the cause of shock and reperfusion are due to the same conditions, the claims of copending application 11/899,611 clearly envision the use of peptide SEQ ID NO: 294 for the treatment of shock.

44. Claims 17-28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 6-7 of copending Application No. 12/121,533. Although the conflicting claims are not identical, they are not patentably distinct from each other because if one practiced the claimed invention of instant claims, one would necessarily achieve the claimed invention of copending application and vice versa.

45. Instant claims are drawn to a method for treating shock comprising administering to a subject in need of such treatment an effective amount of a peptide of Formula II. Claims 23-28 are drawn to a method of treating shock, wherein shock is due to myocardial infarction, vascular surgery...surgical procedures and stroke, and organ dysfunction of grafter organs, and so forth.

46. Claims 6-7 of copending application are drawn to a pharmaceutical composition containing a compound of the general formula (I) and medical use of a compound of the general formula (I). The instant specification discloses that diseases belonging to the

group are those in context with autoimmunity…a healing effect harmful to the tissue…important to the treatment of shock (see p. 11).

47. Therefore, if one of ordinary skill in the art practiced the claimed invention of the instant claims, one would necessarily achieve the claimed invention of copending application 12/121,533, and vice versa.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Applicant's Arguments

48. Applicant has not provided any arguments for this obviousness rejection.

49. As described above in the body of the rejection, claims 6-7 of copending application are drawn to a pharmaceutical composition and a medical use of a compound of the general formula (I). Since the medical use and the intended use for the pharmaceutical composition is not claimed, the instant specification was examined for the medical use. The instant specification discloses that diseases belonging to the group are those in context with autoimmunity…a healing effect harmful to the tissue…important to the treatment of shock (see p. 11). Since the medical use is for the same purpose as instant claims (shock), the claims of copending application 12/121,533 clearly envision the use of peptide of formula (I) for the treatment of shock.

50. Claims 17-28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-7 of copending Application No. 12/121,544. Although the conflicting claims are not identical, they are

not patentably distinct from each other because if one practiced the claimed invention of instant claims, one would necessarily achieve the claimed invention of copending application and vice versa.

51. Instant claims are drawn to a method for treating shock comprising administering to a subject in need of such treatment an effective amount of a peptide of Formula II. Claims 23-28 are drawn to a method of treating shock, wherein shock is due to myocardial infarction, vascular surgery...surgical procedures and stroke, and organ dysfunction of grafter organs, and so forth.

52. Claims 6-7 of copending application are drawn to a pharmaceutical composition comprising peptide of formula I, medical use of a compound of the general formula (I). The medical use is not defined in the claims. The instant specification discloses that diseases belonging to this group are those in context with autoimmunity… a healing effect harmful to the tissue…important to the treatment of shock (see p. 11).

53. Therefore, if one of ordinary skill in the art practiced the claimed invention of the instant claims, one would necessarily achieve the claimed invention of copending application 12/121,544, and vice versa.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Applicant's Arguments

54. Applicant has not provided any arguments for this obviousness rejection.

55. As described above in the body of the rejection, claims 6-7 of copending application are drawn to a pharmaceutical composition and a medical use of a compound of the general formula (I). Since the medical use and the intended use for the pharmaceutical composition is not claimed, the instant specification was examined for the medical use. The instant specification discloses that diseases belonging to the group are those in context with autoimmunity…a healing effect harmful to the tissue…important to the treatment of shock (see p. 11). Since the medical use is for the same purpose as instant claims (shock), the claims of copending application 12/121,544 clearly envision the use of peptide of formula (I) for the treatment of shock.

56. Claims 17-28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 and 4-5 of copending Application No. 12/158,670. Although the conflicting claims are not identical, they are not patentably distinct from each other because if one practiced the claimed invention of instant claims, one would necessarily achieve the claimed invention of copending application and vice versa.

57. Instant claims are drawn to a method for treating shock comprising administering to a subject in need of such treatment an effective amount of a peptide of Formula II. Claims 23-28 are drawn to a method of treating shock, wherein shock is due to myocardial infarction, vascular surgery...surgical procedures and stroke, and organ dysfunction of grafter organs, and so forth.

58. Claims 1-2 and 4-5 of copending application are drawn to a method for treating hemorrhagic shock or the sequels thereof, comprising administering to an animal a peptide comprising the N-terminal sequence GHRPLDKKREEAPSLRPAPPPISGGGYR, that is the same as the instant SEQ ID NO:3.

59. Since the copending application is drawn to a method of treating hemorrhagic shock, if one of ordinary skill in the art practiced the claimed invention of the instant claims, one would necessarily achieve the claimed invention of copending application 12/158,670, and vice versa.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Applicant's Arguments

60. Applicant has not provided any arguments for this obviousness rejection.

61. As described above in the body of the rejection, claims 1-2 and 4-5 of copending application are drawn to a method for treating hemorrhagic shock comprising administering to an animal a peptide comprising the N-terminal sequence GHRPLDKKREEAPSLRPAPPPISGGGYR, the same sequence as instant SEQ ID NO: 3. Since the copending application is drawn to a method of treating hemorrhagic shock, if one of ordinary skill in the art practiced the claimed invention of the instant claims, one would necessarily achieve the claimed invention of copending application 12/158,670, and vice versa.

New Objection

62. Claims 19-22 are objected to for the following reasons: Claims 19-20 recite amino acid sequence DKKREEAPSLRPAPPPISGGGYR. The peptide sequences are missing the sequence identifiers. Claims 21-22 recite amino acid sequence GHRPLDKKREEAPSLRPAPPPISGGGYR. The peptide sequences are missing the sequence identifers. The proper way to claim a peptide sequence is for example, DKKREEAPSLRPAPPPISGGGYR (SEQ ID NO:3) (see 37 CFR 1.821(d)). These errors should be corrected.

63. Claims 19-20 are objected for the following minor informality: There appears to be spelling errors in these claims. Claims 19-20 recite, “Z4 denotes a leucinene residue” The “leucinene” appears to be in error. This should be corrected to “leucine”, for example.

64. Claims 23-28 are objected to for the following minor informality: Claims 23-28 recite, "...wherein the shock is associated with one or more out of the group..." The phrase "one or more out of the group..." appears to be read awkwardly. In order to avoid confusion, the claims should be corrected to read for example, "...with one or more from the group…”

65. Claims 23-28 are objected to for the following minor informality: Claims 23-28 recite, “…acute hemorrhagic respiratory failure caused by infectoius agents…” There appears to be a spelling error with “infectoius agents”. These should be corrected to “infectious agents”.

66. Claims 23-28 are objected to for the following minor informality: Claims 23-28 recite, "…haemorrhagic shock" at line 3 of the claims, "hemorrhagic respiratory failure" at line 4 of the claims, and "haemorrhagic shock" at line 6 of the claims. In order to be consistent in spelling, Applicant should correct "haemorrhagic" to "hemorrhagic".

New Rejection

35 U.S.C. 112, 2nd

67. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

68. Claims 17-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

69. Claim 17 recites, "a peptide derived from the Bbeta chain of the fibrin" which is indefinite. It is unclear what is encompassed by the term "a peptide derived from the Bbeta chain of the fibrin." The specification does not define what is encompassed by the term "a peptide derived from the Bbeta chain of the fibrin". For example, it is unclear what modifications are encompassed within a peptide derived from the Bbeta chain of the fibrin. Because claims 18 and 23-34 depend from indefinite claim 17 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

70. Claim 17 recites, "A method for treating shock comprising administering to a subject in need of such treatment an effective amount of a peptide of Formula II…" It is

unclear what is an "effective amount of a peptide of Formula II" encompasses. The instant specification does not define what an “effective amount of a peptide of Formula II” is. The MPEP states the following: “The common phrase “an effective amount” may or may not be indefinite. The proper test is whether or not one skilled in the art could determine specific values for the amount based on the disclosure. See *In re Mattison*, 509 F.2d 563, 184 USPQ 484 (CCPA 1975)...The phrase "an effective amount" has been held to be indefinite when the claim fails to state the function which is to be achieved and more than one effect can be implied from the specification or the relevant art. *In re Fredericksen* 213 F.2d 547, 102 USPQ 35 (CCPA 1954) (see MPEP 2173.05(c)). Because claims 18-26 depend from indefinite claim 17 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

71. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131

USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 23-28 recite the broad recitation …"wherein the shock is associated with one or more…", and the claim also recites "…in particular through…" which is the narrower statement of the range/limitation.

Obviousness Double Patenting

72. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

73. Claims 17-28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 7,494,973. Although the conflicting claims are not identical, they are not patentably distinct from each other because if one practiced the claimed invention of instant claims, one would necessarily achieve the claimed invention of copending application, and vice versa.

74. Instant claims are drawn to a method for treating shock comprising administering to a subject in need of such treatment an effective amount of a peptide of Formula II.

75. Claims 1-3 of US Patent No. '973 are drawn to a method of treating rejection of a transplanted tissue in a subject comprising administering to the subject a peptide of SEQ ID NO: 294. The specification of the reference teaches that the invention consist in the preparation of pharmaceutical compositions for the therapy or prevention of local and/or generalized inflammation in the body in case of infectious genesis, based upon an auto-immune reaction, based upon a rheumatic disease, based upon a disorder in the immune system, based upon genetic disease, for the prevention and/or therapy of the rejection occurring after organ transplants, and so on (see column).

76. The instant claims 23-28 claim that the shock is associated with one or more of the group comprising bacterial toxins, hemorrhagic shock following viral infection…infectious agents or autoimmune diseases, organ failure after organ injury…vascular surgery, clamping of organs…organ dysfunction of grafted organs, and so on.

77. Therefore, if one practiced the claimed invention of the instant claims, one would necessarily achieve the claimed invention of the U.S. Patent No. '973 and vice versa.

Conclusion

78. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). No claim is allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Julie Ha/
Examiner, Art Unit 1654

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654